Seizure Disorders

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Seizure ≠ Epilepsy

- Seizure – a discrete clinical event that results in the abnormal discharge of a set of neurons in the brain
- Epilepsy – recurrent seizure activity (>2), often unprovoked without an identifiable cause
- Status Epilepticus – 1 prolonged seizure > 30 minutes or 2 or more seizures in which the patient does not regain consciousness

Epilepsy

- Affects nearly 2.3 million Americans
- 181,000 new cases diagnosed each year
- Most often presents in infancy and childhood
  - 0.5 % - 1% children have epilepsy
- 10% of US population experience seizure in lifetime
- 3% diagnosed with epilepsy before the age of 75
- Risk increased with traumatic brain insults / injuries
- > $12.5 billion is estimated in indirect and direct costs
- Prior to 1993 (felbamate) no new AED's for 15 years
- Eight new AED's released in 1990's

Childhood Epilepsy

- Many children become seizure free
- Most seizures are brief
- Rarely do seizures cause long-term brain damage without neurologic insult
- Medications may cause long-term side effects

International League Against Epilepsy Classifications

- Acute symptomatic
  - Result from head trauma or infection
- Remote symptomatic
  - No immediate cause, but prior brain injury, MR, or cerebral palsy
- Cryptogenic
  - Occur in otherwise normal individuals
- Idiopathic
  - Genetic association

Recurrence Risk Factors

- Abnormal EEG
- Seizure occurs during sleep
- No clear association of seizure type
- No association with seizure length
- No association with age of onset

Epilepsy Etiology

- Defects in mediator inhibition
  - GABA
- Enhanced excitatory neurotransmission
  - Glutamate / Aspartate
  - NMDA / AMPA Receptors
- Defects in ion transport across neuronal membranes
  - Sodium / Calcium
- Pediatric Related Issues
  - Hypoxia
  - Metabolic Disturbances

Epileptic Seizure Classification

- Partial Seizures
  - Simple partial
    - With motor symptoms
    - With somatosensory symptoms
    - With autonomic symptoms
    - With psychic symptoms
  - Complex partial
  - Partial with secondary generalization
- Generalized Seizures
  - Absence
  - Myoclonic
  - Clonic
  - Tonic
  - Tonic-Clonic
  - Atonic

Unclassified Seizures

- Benign Rolandic Epilepsy
  - Inherited syndrome
  - Occurs ages 3 – 15, outgrown by age 16
  - Most seizures occur during sleep
- West Syndrome
  - Infantile spasms, developmental regression
  - Peak onset 4 – 8 months of age
  - Recurrent brief myoclonic seizures
- Lennox-Gastaut
  - Occurs 1 – 8 years of age
  - Mixture of seizure types
  - High frequency of status epilepticus
  - 40% - 80% are mentally retarded

Taking a Seizure Disorder History

- Identifiable source (infection /trauma/med)
- Precipitating event (stress)
- Age of onset / frequency
- EEG patterns
- Severity
- Family history
- Current medications
- Get the before, during, and after…..

When to Treat ??

- After two or more seizures.
- Treat after first seizure if:
  - Idiopathic and abnormal EEG
  - Symptomatic and abnormal EEG
  - Prior neurologic abnormality
  - Positive family history

Treatment Goals

- Prevent occurrence of seizures
  - Decrease frequency and severity
- Prevent or reduce drug side effects and drug interactions
- Prevent the development of neurologic changes
- Improve the patient's quality of life
  - Provide cost-effective care (limit polypharmacy)
  - Ensure patient satisfaction
  - Prevent toxicity

Seizure Specific Treatment Options

Partial Seizures:

Simple Partial
Complex Partial
Secondary Generalized

First Line Agents:

Carbamazepine
Phenytoin
Valproic Acid
Lamotrigine
Oxcarbazepine

Second Line Agents:

Gabapentin
Tiagabine
Topiramate
Phenobarbital
Primidone
Levetiracetam
Zonisamide

Seizure Specific Treatment Options: Generalized Seizures

Generalized Seizure	First-Line	Second-Line
Absence	Ethosuximide, Valproic Acid	Lamotrigine, Clonazepam
Myoclonic	Valproic Acid	Lamotrigine, Clonazepam
Atonic	Valproic Acid	Lamotrigine
Tonic, Clonic, Tonic-Clonic	Carbamazepine, Oxcarbazepine, Valproic Acid	Lamotrigine, Phenobarbital, Primidone, Phenytoin, Topiramate

Targets for Treatment

Target / Mechanism	**Effect**
Sodium Channels	Decrease action potential frequency
Calcium Channels	
T Type	Decrease thalamocortical reverbs
L Type	Decrease cortical excitation
N Type	Decrease neurotransmitter release
Enhanced GABA Transmission	Increased Inhibition
Increased $GABA_A$ Receptor Activity	
Increased GABA Synthesis	
Decreased GABA Reuptake	
Increased Serotonin Release	
Decreased Glutamate Transmission	Decreased Excitation
Inhibit receptor / decrease release	

B Gidal, CPNP, Charleston, SC, 2003.

Proposed Mechanism of Action

AED	Na Channel	Ca Channel	GABA	NMDA
Phenobarbital	+		+	AMPA/KA
Phenytoin	+++	L Type	+	+/- NMDA
Carbamazepine	+++	L Type	↑ 5HT	NMDA
Oxcarabazepine	+++	N Type		
Valproate	+++	T Type	↑ Synthesis	
Felbamate	+	L Type	+	Blocks NMDA

Proposed Mechanism of Action

AED	Na Channel	Ca Channel	GABA	NMDA
Gabapentin	?	L Type	↑Synthesis ↑ 5HT	↓ Glutamate Release
Lamotrigine	+++	N Type	+	↓ Glutamate Release
Levetiracetam	?	?	?	?
Topiramate	+	L Type		Blocks KA
Tiagabine			↓ Reuptake	
Zonisamide	+	L / T Type		

Why Does Treatment Fail ??

- Inappropriate treatment
  - Select the wrong drug
- Inappropriate dose
- Poor compliance / lack of education
  - Drug storage issues (CBZ)
  - Drug administration issues (phenytoin susp)
- Drug interactions
- Seizure refractoriness

When to Stop Treatment ??

- Seizure free 2 to 5 years
- Normal neuro exam / normal IQ
- Normal EEG
- Epilepsy of single seizure type
- No juvenile or myoclonic epilepsy

How to Stop Treatment ??

- Slow titration off over months:
  - Carbamazepine ↓ 100 mg Q 4 weeks
  - Ethosuximide ↓ 250 mg Q 4 weeks
  - Phenobarbital ↓ 30 mg Q 4 weeks
  - Phenytoin ↓ 50 mg Q 4 weeks
  - Valproate ↓ 250 mg Q 4 weeks

Treatment Options

Older Treatment Options

- Valproate (Depakote / Depakote ER®)
- Carbamazepine (Tegretol®)
- Phenytoin (Dilantin®)
- Phenobarbital
- Primidone (Mysoline®)
- Ethosuximide (Zarontin®)

VALPROATE MECHANISM

- Inhibits GABA transaminase and succinic semi-aldehyde dehydrogenase catabolism of GABA
- Increased brain GABA content
- Enhanced postsynaptic GABA effects
- Activates GABA synthesis
- Efficacy in Partial, Generalized, and Absence

Post RM. J Clin Psychiaty, 1989.
Fawcett J. J Clin Psychiatry, 1989.

Valproate Availability

- Tablets
  - 125 mg, 250 mg, and 500 mg
- Extended Release Tablets
  - 250 mg and 500 mg
- Sprinkle Capsules
  - 125 mg
- Syrup
  - 250 mg per 5 ml

Valproate Dosing

- Starting Dose
  - 5 – 15 mg/kg/day (Q Day to TID)
- Maintenance Dose
  - 30 – 60 mg/kg/day
- High-Risk Patients
  - Don’t use in < 2 years of age
    - Mentally retarded
    - Inborn metabolic problems

Valproate Monitoring

- **General medical history**
- **Chemistry profile**
  baseline and every 6 months
- **Pregnancy test**

Serum concentration

maintain 45-125 mcg/ml

CBC with differential

baseline and every 6 months

Liver function tests

baseline and every 6 months

American Psyciatric Association Practice Guidelines, 1994.

Valproate Side Effects

DOSE RELATED

- Benign increase in LFT's
- Tremor
- Sedation
- Alopecia (usually transient)
- GI upset (anorexia, nausea, vomiting, diarrhea)
- Leukopenia / Thrombocytopenia
- Increased appetite
- Weight gain

American Psychiatric Association Practice Guidelines, 1994.

Valproate Side Effects

IDIOSYNCRATIC

- Polycystic ovaries
- Hyperandrogenism
- Hepatic failure (do not use in children < 2) [a]
- Pancreatitis (mentally retarded)[b]
- Agranulocytosis

American Psychiatric Association Practice Guidelines, 1994.

[a] Pellock JM. Neurology, 1991.

[b] Buzar AD, et al. J Clin Psychiatry, 1995.

Valproate Drug Interactions

- Hepatically metabolized drugs

  increased serum concentraions
- Protein bound drugs

  increased effects of warfarin and aspirin
- Phenytoin

  increased free concetrations of phenytoin

Carbamazepine

increased free carbamazepine and epoxide levels

SSRI's

increased valproate concentrations

McEvoy G. AHFS Drug Information, 1993.

Carbamazepine Mechanism

- Kindling at amydala
- Alpha-2 adrenergic stimulation
- Potentiation of $GABA_B$
- Sodium channel stabilization and enhances potassium conductance
- Efficacy in complex partial, partial, and generalized seizures
- Not effective for infantile spasms

Post RM. J Clin Psychiatry, 1989.
Keck PE. J Clin Psychiatry, 2002.

Carbamazepine Availability

- Tablets
  - 200 mg
- Chewable Tablets
  - 100 mg
- Extended Release Tablets
  - (Tegretol XR) 100 mg, 200 mg, 400 mg
- Extended Release Capsules
  - (Carbatrol) 200 mg and 300 mg
- Suspension
  - 100 mg / 5 ml

Carbamazepine Dosing

- < 6 years of age
  - Start: 10 – 20 mg/kg/day (TID – QID)
  - Maintenance: up to 35 mg/kg/day (TID-QID)
- 6 – 12 years old
  - 100 mg po bid
- > 12 years of age
  - 200 mg po bid
- Target Range: 4 – 12 mcg/ml

Carbamazepine Monitoring Parameters

- **General medical history and physical exam**

  baseline with emphasis on history of dyscrasias or liver disease
- **CBC with differential and platelet count**

  every 2 weeks in first 2 months of treatment and then every 3 months if normal
- **Liver function test**

  every 2 weeks in first 2 months of treatment and then every 3 months if normal
- **Renal function test**
- **Serum electrolytes**
- **Serum concentrations**

  5 days after dosage changes until stable

American Psychiatric Association Practice Guidelines, 1994.

Carbamazepine Side Effects
DOSE RELATED

- Diplopia
- Blurred vision
- Fatigue
- Nausea
- Ataxia

Skin rash
Leukopenia
Thrombocytopenia
Hyponatremia (6%-31%)
LFT increases (5%-15%)

American Psychiatric Association Practice Guidelines, 1994.

Carbamazepine Side Effects
IDIOSYNCRATIC

- Agranulocytosis
- Aplastic anemia
- Hepatic failure
- Exofoliative dermatitis (e.g. Stevens-Johnson Syndrome)
- Pancreatitis

American Psychiatric Association Practice Guidelines, 1994.

Phenytoin

- Increases efflux and decreases influx of sodium
- Efficacy in Generalized and Partial Seizures
- Maintenance dosing
  - 4-5 mg/kg/day (2 divided doses)
  - Target serum concentration 5 – 20 mcg/ml
  - Delayed dosage adjustment schedule
- Side effects
  - Nystagmus, ataxia, sedation, mental changes, gum hyperplasia, nausea, vomiting, hirsutism

Phenytoin Pediatric Dosing

- 6 months – 3 years
  - 8 – 10 mg/kg/day
- 4 – 6 years
  - 7.5 – 9 mg/kg/day
- 7 – 9 years
  - 7 – 8 mg/kg/day
- 10 – 16 years
  - 6 – 7 mg/kg/day
- Maintenance Dosing: 4 – 10 mg/kg/day

** Some patients may require TID dosing.

Phenytoin Availability

- Suspension
  - 125 mg / 5 ml
- Capsules
  - Extended Release – 30 mg and 100 mg
  - Immediate Release – 100 mg
- Chewable Tablets
  - 50 mg
- Injection
  - 50 mg/ml

Phenobarbital

- Potentiates GABA and inhibits glutamate
- Efficacy in generalized and partial seizures
- Desired Therapeutic Range: 15 – 40 mcg/ml

Phenobarbital

- Dosing: titrate to response / 2-3 week delay in serum concentration
- Infants
  - 5 – 8 mg/kg/day (1-2 divided doses)
- Children 1 – 5 years
  - 6 – 8 mg/kg/day (1-2 divided doses)
- Children 5 – 12 years
  - 4 – 6 mg/kg/day (1-2 divided doses)
- Side Effects
  - Sedation, behavior changes, cognitive impairment, hyperactivity, irritability

Phenobarbital Availability

- Tablets
  - 15 mg, 16 mg, 30 mg, 32 mg, 60 mg, 65 mg, 100 mg
- Elixir
  - 20 mg / 5 ml
- Injection

Why New AED's ??

- 25 - 30% fail to respond to traditional therapy
- Large percentage of failures are due to intolerability
- 25-30% response rate in those once considered refractory

New Treatment Options

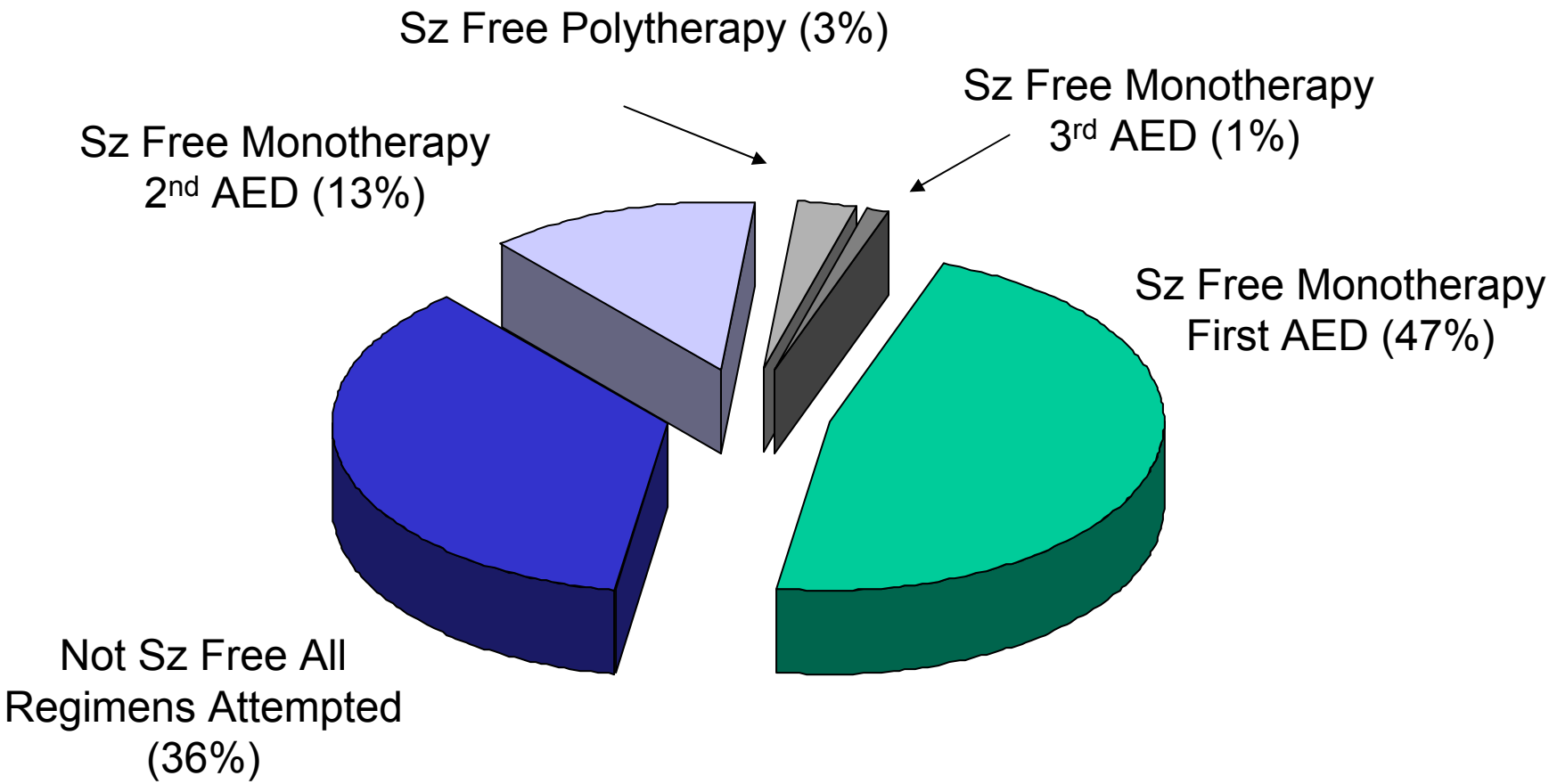
- Felbamate (Felbatol®, 1993)
- Gabapentin (Neurontin®, 1994)
- Lamotrigine (Lamictal®, 1995)
- Topiramate (Topamax®, 1996)
- Tiagabine (Gabitril®, 1997)
- Oxcarbazepine (Trileptal®, 2000)
- Zonisamide (Zonegran®, 2000)
- Levetiracetam (Keppra®, 1999)
- Fosphenytoin (Cerebyx®)

Efficacy of the New AED's

- Similar in clinical trials
  - > 50% reduction in 25% of patients
  - 100% seizure control not likely as monotherapy
  - Acute side effect profiles similar to older AED's

Marson AG, et al. Epilepsia 1997; 38: 859-880.

Success of AED Regimens



Kwan and Brodie, NEJM, 2000.

Felbamate

- Approved for use in US in 1993
- Indications
  - partial seizures in adults with or without secondary generalization
  - adjunctive treatment of partial and generalized seizures in children with LGS
- Aplastic Anemia Risk 20 X greatear than with carbamazepine (risk > in first 6 months)
- Reserved for refractory drug resistant epilepsy

Felbamate Availability

- Tablets
  - 400 mg
  - 600 mg
- Suspension
  - 600 mg per 5 ml

Felbamate Side Effects

- CNS
- Hematologic
- GI

- Headache, diplopia, dizziness, insomnia
- Aplastic anemia
- Nausea, vomiting, anorexia, hepatotoxicity

**** <u>Special Monitoring</u>**

Felbatol Registry

Baseline Glutathione Level/CBC/LFT(1-2 weeks)

Felbamate Dosing

- Adults
  - 1200 mg/day usually divided TID, increase by 1200 mg/day per week to 2400-3600 mg/day
- Pediatrics
  - 15 mg/kg/day increase to max of 45 mg/kg/day (dosed TID or QID)

- Level: 40-100 mg/L

Gabapentin

- Released in US in 1994
- Anticonvulsant, antinociceptive, anxiolytic, neuroprotective agent
- MOA: enhancement of nonsynaptic GABA release and inhibition of voltage dependent sodium currents
- Indications:
  - adjunctive treatment of partial and secondarily generalized seizures in patients > 12 years of age
  - Adjunctive for partial seizures ages 3 – 12 years
- Well-tolerated, renally eliminated, no significant drug-drug interactions or hepatic enzyme induction/inhibition properties
- Increased efficacy with increased dose ?? -- smaller more frequent dosing may increase efficacy

Gabapentin Availability

- Capsules
  - 100 mg
  - 300 mg
  - 400 mg
- Tablets
  - 600 mg
  - 800 mg
- Solution

Gabapentin Side Effects

- CNS
  - Somnolence, ataxia, dizziness, fatigue, tremor, headache, aggression, nystagmus
- Other
  - Weight gain

Gabapentin Dosing (Adult)

- Day 1 100 mg po tid
- Day 2 300 mg po bid
- Day 3 300 mg po tid

  Increase 300-400 mg tid per day as tolerated to target dose

- Range 900-1800 mg/day

  (2400-3600 mg tolerated well)
- Level 4-16 mg/L

Gabapentin Dosing (Pediatric)

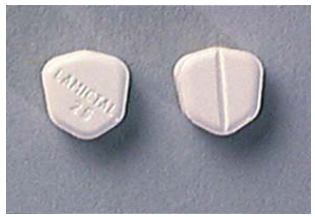
- 3 to 12 years of age
  - 10 – 15 mg/kg/day
- Effective Doses
  - 3 to 4 years of age
    - 40 mg/kg/day
  - 5 years of age and older
    - 25 – 35 mg/kg/day

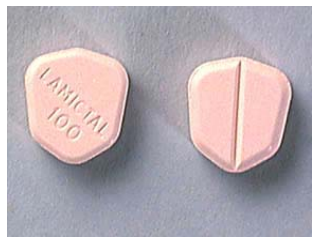
Lamotrigine

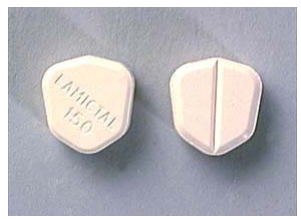
- Primary MOA: blockade of voltage dependent sodium channels, stabilizes neuronal membranes, and inhibits glutamate release
- Indications:
  - Adjunctive treatment of partial seizures
  - Adjunctive in generalized seizues of Lennox-Gastaut Epilepsy
  - Adult patients with partial seizures converted to monotherapy with enzyme inducing AED

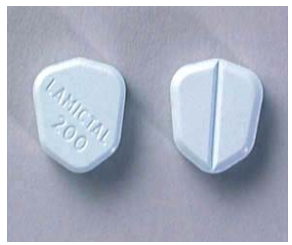
Lamotrigine Availability

- Tablets
  - 25 mg
  - 100 mg
  - 150 mg
  - 200 mg

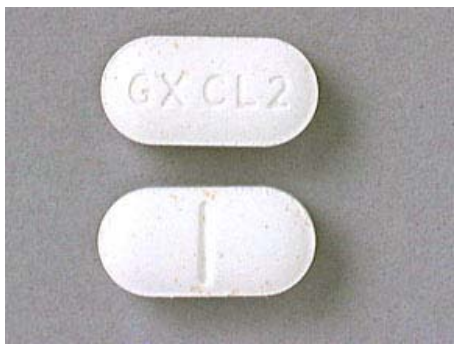








- Chewable Tablets
  - 2 mg
  - 5 mg
  - 25 mg



Lamotrigine Side Effects

- CNS
- GI
- Other

- Dizziness, ataxia, drowsiness, headache, diplopia
- Nausea, vomiting, pancreatitis
- Rash [10-12%]; (Stevens-Johnson Syndrome, 1%)

** Rash risk increases in children, rapid titration, and concurrent use with valproate.

Lamotrigine Dosing

- AED regimen with valproic acid (> 12yo)
  - Weeks 1 and 2 give 25 mg every other day
  - Weeks 3 and 4 give 25 mg every day
  - Increase by 25-50 mg every 1-2 weeks to MD of 100-200 mg/day
- AED regimen with EIAED (without valproic acid) [>12 yo]
  - Weeks 1 and 2 give 50 mg/day
  - Weeks 3 and 4 give 100 mg/day (BID)
  - Increase by 100 mg/day every 1-2 weeks to MD of 300-500 mg/day (BID)

Lamotrigine Dosing (Children)

- 2 - 12 years old with Divalproex
  - Weeks 1 and 2
    - 0.15 mg/kg/day in 1-2 divided doses, round down to nearest whole tablet
  - Weeks 3 and 4
    - 0.3 mg/kg/day in 1-2 divided doses, round down to nearest whole tablet
  - Maintenance Dose
    - 1 – 5 mg/kg/day (max 200 mg/day in 1-2 divided doses)

Lamotrigine Dosing (Children)

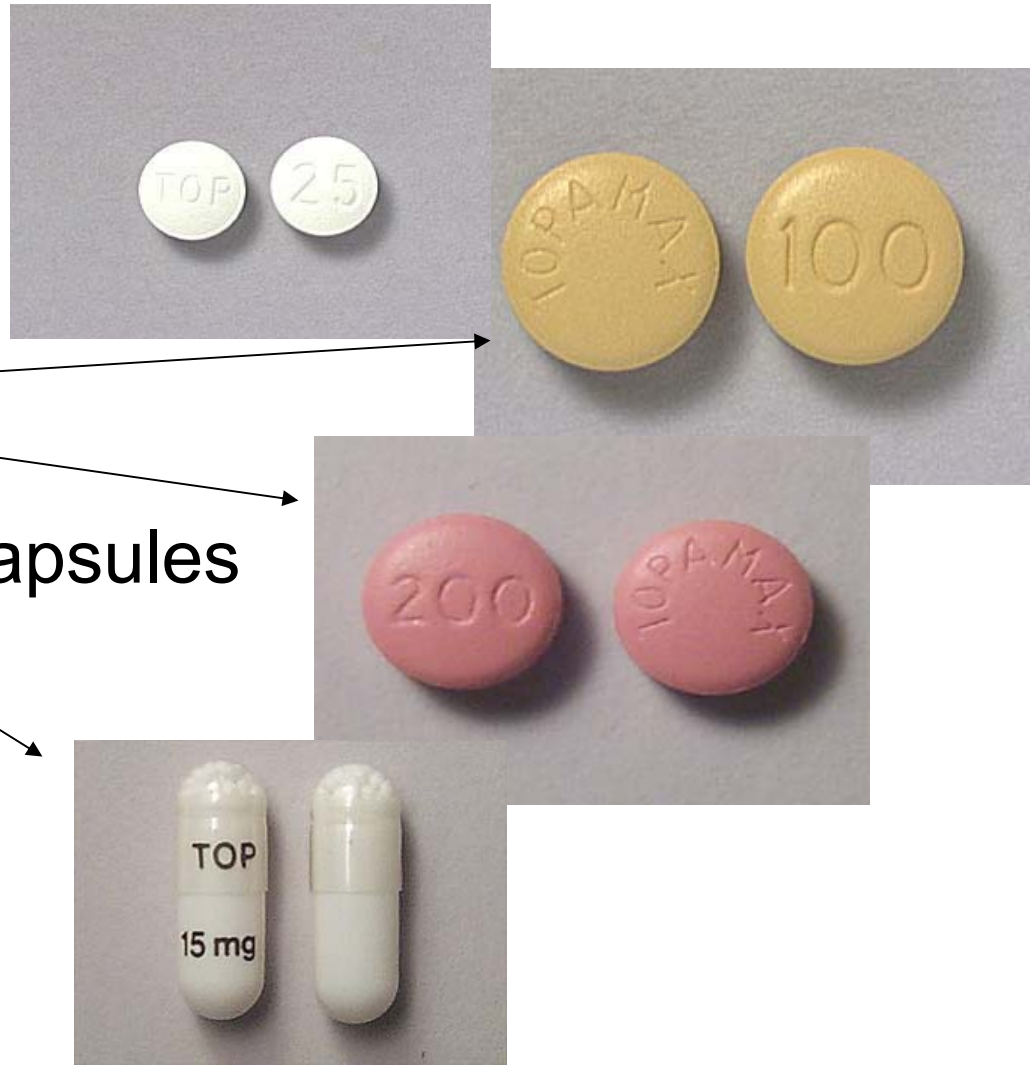
- Lamotrigine added to EIAED's (without valproic acid)
  - Weeks 1 and 2
    - 0.6 mg/kg/day in 2 divided doses, round down to nearest whole tablet
  - Weeks 3 and 4
    - 1.2 mg/kg/day in 2 divided doses, round down to nearest whole tablet
  - Maintenance Dose
    - 5 – 15 mg/kg/day (max 400 mg/day dosed BID)

Topiramate

- MOA: blockade of voltage dependent sodium channels, potentiation of GABA, and glutamate antagonism
- Indications: (“broad-spectrum”) adjunctive treatment of partial and generalized tonic-clonic seizures in adults and children ages 2 to 16 years
- Possible role in childhood epilepsy (LGS, infantile spasms)
- Increases attention and interaction
- Induces metabolism of oral contraceptives

Topiramate Availability

- Tablets
  - 25 mg
  - 100 mg
  - 200 mg
- Sprinkle Capsules
  - 15 mg
  - 25 mg



Topiramate Side Effects

- CNS
- GI
- Renal
- Other

- Dizziness, ataxia, somnolence, cognitive
- Weight loss
- Nephrolithiasis
- Parasthesias

Topiramate Dosing (Adults)

- Week 1 50 mg po q hs
- Week 2 50 mg po bid
- Week 3 50 mg po q am and 100 mg q hs
- Week 4 100 mg po bid
- Week 5 100 mg po q am and 150 mg q hs
- Week 6 150 mg po bid
- Week 7 150 mg po q am and 200 mg q hs
- Week 8 200 mg po bid
  - **More conservative dosing at 25 mg/week increase.

Topiramate Dosing (Children)

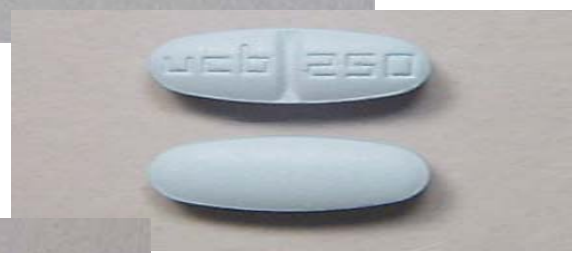
- **Children 2 to 16 years of age**
  - 1 – 3 mg/kg/day starting dose (< 25 mg)
  - Increase by 1 – 3 mg/kg/week until 8-10 mg/kg/day divided BID
  - Dosing Range: 5 – 9 mg/kg/day in 2 divided doses

Tiagabine

- MOA: selectively inhibits reuptake of GABA into neurons and glial cells
- Indications:
  - adjunctive treatment of partial and secondary generalized seizures (possible monotherapy)
  - Exacerbates absence and myoclonic seizures
- Possible niche with treatment of infantile spasms

Tiagabine Availability

- Tablets
  - 4 mg
  - 12 mg
  - 16 mg



Tiagabine Side Effects

- CNS
  - Dizziness, somnolence, headache

Tiagabine Dosing (> 18 yo)

- Week 1 4 mg/day
- Week 2 4 mg po bid
- Week 3 4 mg po tid
- Week 4 8 mg po bid
- Week 5 20-24 mg/day
- Week 6 24-32 mg/day (MAX 56 mg/day)

**(Dose BID-QID and Take with food)

Tiagabine Dosing (Children)

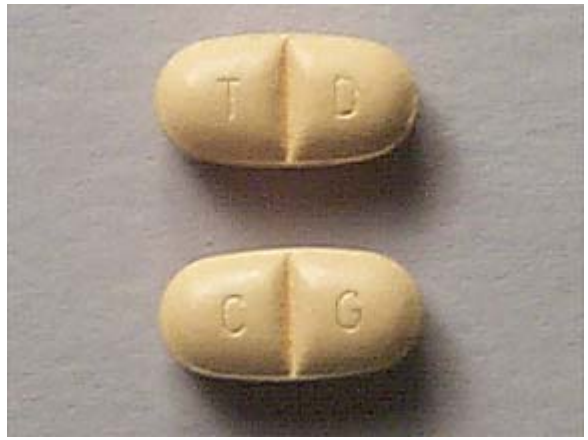
- **Pediatrics: 0.25-1.5 mg/kg/day**
  - 0.1 mg/kg/day usual starting dose
  - 1.5 mg/kg/day usual maintenance dose
- **12 to 18 years of age**
  - Initiate at 4 mg once daily. Increase by 4 to 8 mg at weekly intervals.
  - Increase per clinical response and tolerability up to 32 mg/day.

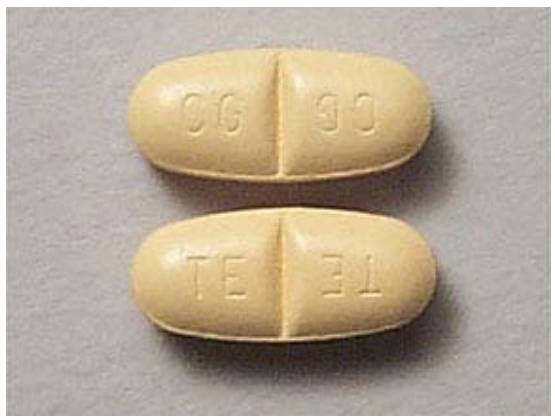
Oxcarbazepine

- 10 Keto-analog of carbamazepine
- Rapidly transformed to 10-monohydroxy derivative (pharmacologically active)
- Indication: Adjunct or monotherapy for partial seizures in adults or adjunct therapy in partial seizures in children as young as 4 years of age
- MOA: primarily blocks voltage dependent sodium channels
- Dose 1.5 X carbamazepine dose
- ?? Cytochrome P450 Interactions: induces 3A4, inhibits 2C19
- No autoinduction, no epoxide formation
- Cross-sensitivity with carbamazepine 20-30%
- Decreased efficacy of oral contraceptives

Oxcarbazepine Availability

- Oral Suspension
  - 300 mg / 5 ml
- Tablets
  - 150 mg
  - 300 mg
  - 600 mg





Oxcarbazepine Side Effects

- CNS
- GI
- Dermatologic
- Other

- Dizziness, ataxia, somnolence, fatigue
- Nausea, vomiting, anorexia
- Rash
- hyponatremia

Oxcarbazepine Dosing

- Adult
  - Initiate 600 mg/day (BID), increase by 600 mg/day to target MD = 1200-2400 mg/day dosed on BID schedule
- Pediatric (Age 4 – 16 years)
  - 8-10 mg/kg/day, NTE 600 mg/day
  - (20-29 kg MD = 900 mg/day)
  - (29.1-39 kg MD = 1200 mg/day)
  - (> 39 KG MD = 1800 mg/day)

Zonisamide

- Marketed in Japan since 1989
- MOA: blockade of sodium and calcium channels (also possible carbonic anhydrase)
- Indication: adjunctive therapy in partial seizures in adults (>16 yo)
- Sulfonamide…..sulfa hypersensitivity
- Two confirmed reports of agranulocytosis

Zonisamide Availability

- Zonegran 100mg-red and white capsules

Zonisamide Side Effects

- CNS
- GI
- Renal

- Dizziness, somnolence, headache, cognitive impairment
- Anorexia, weight loss, nausuea
- Nephrolithiasis

Zonisamide Dosing

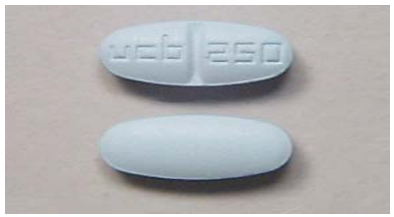
- Adult
  - 100 mg/day, increase by 100 mg/day every 2 weeks (Max. 400 mg/day)
- Pediatric
  - 2-4 mg/kg/day
- Level: 10-40 mg/L

Levetiracetam

- Approved by FDA < 10 months for adjunctive treatment of partial seizures in adults
- No protein binding, no active metabolites
- Not metabolized via CYP450 system
- Excreted unchanged in the urine (66%)
- May be initiated at effective dose
- FDA approved for partial onset seizures in adults

Levetiracetam Availability

- Keppra 250 mg--blue, oblong tablets



- Keppra 500 mg--yellow, oblong tablets

- Keppra 750 mg--orange, oblong tablets

Levetiracetam Side Effects

- CNS
- Somnolence, dizziness
- Other
- Weight loss

Levetiracetam Dosing

- Adult
  - 500 mg po bid, increase by 1000 mg q 1-2 weeks (Max. 3000 mg/day)
- Pediatric
  - 20 mg/kg/day (dosed on BID schedule)

Vigabatrin

- Not approved in the US due to toxicity
- Indications outside of US:
  - partial seizures in adults
  - effective in pediatric population (infantile spasms)
- MOA: non-reversible GABA-aminotransaminase inhibitor

Vigabatrin Side Effects

- CNS
- GI
- Other
- Psychosis
- Weight gain
- Visual field constriction

New Formulations of “Old” AED’s

- Tegretol-XR®
  - Gradual release during GI transit
- Carbatrol®
  - Multicomponent capsule of immediate, extended, and enteric -released beads
- Diastat®
  - Rectally administered gel (diazepam)
- Depacon®
  - IV form of valproic acid for use in phenytoin allergic patients

Cytochrome P450 and AED Drug Interactions

Drug	**CYP1A2**	**CYP2C9**	**CYP2C19**	**CYP3A4**
Substrates	CBZ	Phenytoin Phenobarb Valproate	Phenytoin Diazepam	CBZ Tiagabine Zonisamide
Inhibitors		Valproate	Felbamate	(grapefruit juice)
Inducers	(cigarette smoking) (grilled meats)	CBZ Phenobarb Phenytoin	CBZ Phenobarb Phenytoin	CBZ Phenobarb Phenytoin

Cloyd, et al. *Pharmacotherapy,* August 2000.

Unanswered Questions

- Comparative efficacy and safety
  - > efficacy with topiramate and vigabatrin
  - Lamotrigine and gabapentin better tolerated
- Safety in pregnancy and lactation
  - Pregnancy category C
- Cost effectiveness
  - Must show greater efficacy in specific seizure types, have better tolerability, and evidence of increased safety.
- % of Patients that become seizure free
- Decrease mortality rates

“The most expensive drug therapy is the one that doesn’t work.”